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Differing prognostic value of pulse pressure in patients with heart failure with reduced or preserved ejection fraction: results from the MAGGIC individual patient meta-analysis

Colette E. Jackson, Davide Castagno, Aldo P. Maggioni, Lars Køber, Iain B. Squire, Karl Swedberg, Bert Andersson, A. Mark Richards, Antoni Bayes-Genis, Christophe Tribouilloy, Joanna Dobson, Cono A. Ariti, Katrina K. Poppe, Nikki Earle, Gillian Whalley, Stuart J. Pocock, Robert N. Doughty, John J.V. McMurray on behalf of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)

Abstract

Aims Low pulse pressure is a marker of adverse outcome in patients with heart failure (HF) and reduced ejection fraction (HF-REF) but the prognostic value of pulse pressure in patients with HF and preserved ejection fraction (HF-PEF) is unknown. We examined the prognostic value of pulse pressure in patients with HF-PEF [ejection fraction (EF) ≥ 50%] and HF-REF.

Methods and results Data from 22 HF studies were examined. Preserved left ventricular ejection fraction (LVEF) was defined as LVEF ≥ 50%. All-cause mortality at 3 years was evaluated in 27 046 patients: 22 038 with HF-REF (4980 deaths) and 5008 with HF-PEF (828 deaths). Pulse pressure was analysed in quintiles in a multivariable model adjusted for the previously reported Meta-Analysis Global Group in Chronic Heart Failure prognostic variables. Heart failure and reduced ejection fraction patients in the lowest pulse pressure quintile had the highest crude and adjusted mortality risk (adjusted hazard ratio 1.68, 95% confidence interval 1.53–1.84) compared with all other pulse pressure groups. For patients with HF-PEF, higher pulse pressure was associated with the highest crude mortality, a gradient that was eliminated after adjustment for other prognostic variables.

Conclusion Lower pulse pressure (especially <53 mmHg) was an independent predictor of mortality in patients with HF-REF, particularly in those with an LVEF < 30% and systolic blood pressure <140 mmHg. Overall, this relationship between pulse pressure and outcome was not consistently observed among patients with HF-PEF.

Introduction

Elevated pulse pressure is an established marker of adverse outcome in healthy individuals as well as patients with certain types of cardiovascular disease, especially those with hypertension.[1–3] More recently, lower pulse pressure has emerged as an independent predictor of mortality in patients with heart failure (HF).[4–9] This has been demonstrated in patients across the spectrum of symptom severity, and in patients with acute as well as chronic HF. However, studies to date have included only patients with heart failure and reduced left ventricular ejection fraction (HF-REF). Patients with heart failure and preserved left ventricular ejection fraction (HF-PEF) more often have a history of hypertension than patients with HF-REF, and therefore, may be more likely to have an elevated pulse pressure. However, the range of pulse pressures in patients with HF-PEF, compared with HF-REF, is unknown, as is the prognostic importance of pulse pressure in HF-PEF.

We used data from 22 HF studies included in the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) to explore these questions.

Methods

Study design

The design and results of the MAGGIC meta-analysis are described elsewhere.[10] Briefly, observational studies and randomized controlled trials of patients with established HF published up to 2008 were

identified via online databases using the keywords: prognosis, outcome, HF, left ventricle, and preserved. Studies were included if they enrolled patients with HF, reported outcome (all-cause mortality), and did not use left ventricular ejection fraction (LVEF) as criterion for entry to the study. The University of Auckland Human Subjects Ethics Committee approved the original meta-analysis and the study complied with the Declaration of Helsinki. All patients provided written informed consent to participate in the individual studies.

Of 56 potential studies that were identified, investigators from 31 studies provided data on a pre-defined set of variables including demographics, medical history, medical treatment, symptom status, clinical variables, laboratory variables, and duration of follow-up. All-cause death was the only outcome available. Preserved LVEF was defined as ≥50%. Blood pressure (BP) measurement was taken over the brachial artery with a standard sphygmomanometer and recorded at the baseline study visit (at an outpatient visit, at randomization, or during hospitalization depending on the study design). Pulse pressure was defined as the difference between systolic and diastolic pressure. The principal outcome was all-cause mortality at 3 years from hospital discharge or baseline study visit.

Statistical analysis

Measurements of systolic and diastolic BP were available for patients in 22 of the 31 studies included in the MAGGIC meta-analysis. This analysis was performed using data from these 22 studies (the full list of MAGGIC studies is contained in Appendix section and those included in this article are identified by *). Pulse pressure results were analysed in quintiles and Cox proportional hazards models were used to estimate the hazard of pulse pressure according to HF-PEF or HF-REF, adjusted for the previously reported MAGGIC prognostic variables: age, gender, ischaemic aetiology, atrial fibrillation (AF), hypertension, and diabetes. Mortality curves are similarly adjusted for the MAGGIC prognostic variables. To further investigate the relationship with ejection fraction (EF), those in the HF-REF group with a continuous measure of EF were stratified as <30 or 30–49%, and the adjusted model was repeated in these groups. To investigate the independent prognostic significance of pulse pressure and systolic BP, the main model was repeated using these as continuous variables. The relationship between pulse pressure and outcome in the presence of systolic blood pressure (SBP) was evaluated with an interaction term for both HF-PEF and HF-REF. Further analyses were performed in both EF groups, stratifying on SBP <140/≥140 mmHg, using quintiles of pulse pressure. Sensitivity analyses were performed: (i) with New York Heart Association (NYHA) Class (I/II vs. III/IV), (ii) with medications [angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor antagonist, digoxin, and spironolactone], (iii) excluding those patients with AF, and (iv) for acute HF vs. chronic HF. A *P*-value of <0.05 was considered statistically significant. Analyses were performed using SAS v9.2 (SAS Institute, Inc.).

Results

Baseline characteristics according to pulse pressure, overall

The 22 studies included 27 046 patients of whom 22 038 (81.5%) had HF-REF. Complete data for 25 465 patients were available for the multivariable analysis. Overall, the mean (SD) age was 65 (12) years, 71% were male and median [inter-quartile ratio (IQR)] LVEF was 34% (26, 45). Mean (SD) BP was 131 (23)/77 (12) mmHg, resulting in a mean (SD) pulse pressure of 54 (18) mmHg. *Table 1* shows the baseline characteristics of all patients according to quintiles of pulse pressure. There were many differences between patients according to pulse pressure value. Higher pulse pressure was associated with older age, female sex, history of hypertension, history of diabetes mellitus, higher systolic BP, and higher LVEF. These differences were most marked in the highest pulse pressure quintile, compared with the other quintiles. Those with a lower pulse pressure were more likely to be male and younger, to have had a previous myocardial infarction, to have a lower systolic and diastolic BP, reduced LVEF and to be treated with an ACE inhibitor or angiotensin receptor blocker, spironolactone, and digoxin; they were less likely to have a

history of diabetes and hypertension (*Table 1*). There was no difference in β-blocker prescribing according to pulse pressure.

Table 1

Baseline characteristics according to groups defined by quintiles of pulse pressure

Pulse pressure (mmHg)	**Whole group**	**≤39**	**40–49**	**50–55**	**56–68**	**≥69**	***P*-value (test for trend)**
n (22 studies)	25 465	4106	5957	4944	5352	5106	<0.001
Age, years (SD)	65 (12)	60 (12)	63 (12)	65 (11)	67 (11)	70 (10)	<0.001
Women (%)	30	21	25	28	32	42	<0.001
Medical history							
Hypertension	47	32	38	44	54	66	<0.001
Myocardial infarction	51	53	54	52	51	44	<0.001
Atrial fibrillation	16	15	16	17	17	16	0.019
Diabetes	26	20	22	25	30	33	<0.001
Ischaemic aetiology	60	59	63	61	61	57	<0.001
Medication							
ACEi or ARB	69	76	73	70	65	63	<0.001
β-Blocker	43	43	45	43	43	42	0.039
Diuretic	79	82	79	80	77	80	0.009
Spironolactone	19	28	21	18	16	14	<0.001
Digoxin	45	50	47	46	42	39	<0.001
Clinical status							
NYHA class (I or II/III or IV)	60/40	54/46	62/38	61/39	61/39	61/39	
Heart rate (b.p.m.)	78 (17)	80 (17)	78 (16)	77 (16)	77 (16)	77 (17)	<0.001
SBP (mmHg)	131 (23)	106 (12)	118 (12)	128 (12)	128 (12)	160 (19)	<0.001
DBP (mmHg)	77 (13)	75 (11)	75 (11)	77 (12)	77 (12)	79 (15)	<0.001
Pulse pressure (mmHg)	54 (17)	31 (5)	42 (3)	51 (2)	51 (2)	80 (12)	<0.001
LVEF %, median (IQR)	34 (26, 45)	28 (21, 27)	32 (24, 40)	34 (26, 44)	34 (26, 44)	41 (31, 54)	<0.001
HF-PEF (%)	19	9	13	17	22	33	<0.001
All-cause deaths, *n* (%)	5684 (22)	1071 (26)	1250 (21)	1033 (21)	1130 (21)	1200 (24)	0.029

Values in parentheses are standard deviations for continuous variables or percentages for discrete variables. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; b.p.m., beats per minute; DBP, diastolic blood pressure; HF-PEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure.

Baseline characteristics according to pulse pressure, by left ventricular ejection fraction stratum

Of the 27 046 patients, 5008 (18.5%) patients had HF-PEF. The proportion of patients with HF-PEF increased with the higher quintiles of pulse pressure: for example, 9% of the lowest quintile of pulse pressure had HF-PEF compared with 33% in the highest quintile (*Table 1*). The mean (SD) pulse pressure was 52 (6) and 62 (4) mmHg for patients with HF-REF and HF-PEF, respectively. *Table 2* shows the baseline characteristics according to quintiles of pulse pressure and stratified according to HF-REF or HF-PEF. The differences in baseline characteristics overall, described above, were also apparent within each LVEF stratum.

Table 2

Baseline characteristics according to groups defined by quintiles of pulse pressure, in patients with reduced and preserved EF

	HF-REF					***P*-value (test for trend)**	**HF-PEF**					***P*-value (test for trend)**
Pulse pressure (mmHg)	**≤39**	**40–45**	**46–53**	**54–64**	**≥64.5**		**≤45**	**46–55**	**56–64**	**65–78**	**79–164**	
n (22 studies)	3750	4455	4011	4324	4118		966	978	938	962	963	
Age, years (SD)	60 (12)	62 (12)	65 (11)	67 (10)	69 (10)	<0.001	65 (13)	67 (12)	69 (11)	71 (10)	73 (10)	<0.001
Women (%)	19	22	25	26	34	<0.001	39	45	46	53	61	<0.001
Medical history												
Hypertension	31	34	42	50	60	<0.001	47	56	64	71	78	<0.001
MI	55	57	56	56	51	<0.001	33	34	30	32	30	0.030
Atrial fibrillation	14	15	15	16	14	0.456	26	26	24	24	17	<0.001
Diabetes	20	21	25	30	32	<0.001	19	23	28	30	35	<0.001
Ischaemic aetiology	60	65	63	65	62	<0.001	50	51	48	48	49	0.219
Medication												
ACEi or ARB	79	78	76	72	70	<0.001	44	44	44	42	53	0.001
Beta-blocker	42	44	44	43	42	0.369	46	45	42	43	41	0.016
Diuretic	83	80	81	79	81	0.047	72	73	74	75	78	0.001
Spironolactone	29	22	20	18	14	<0.001	17	13	14	15	10	<0.001
Digoxin	51	50	50	46	44	<0.001	30	31	28	31	27	0.108
Clinical status												
NYHA class (I or II/III or IV)	54/46	59/41	60/40	61/39	60/40	<0.001	67/33	69/31	65/35	62/38	63/37	<0.001
Heart rate (b.p.m.)	80 (17)	77 (16)	77 (16)	77 (16)	78 (17)	<0.001	77 (18)	76 (17)	77 (18)	75 (17)	77 (20)	<0.001
SBP (mmHg)	106 (12)	116 (11)	126 (12)	136 (12)	156 (18)	<0.001	115 (14)	129 (12)	131 (20)	150 (13)	172 (22)	<0.001
DBP (mmHg)	75 (11)	75 (11)	76 (12)	77 (12)	79 (14)	<0.001	77 (12)	78 (12)	79 (13)	79 (13)	80 (17)	<0.001
Pulse	31 (5)	41 (2)	50 (1)	59 (3)	77	<0.001	38 (6)	51 (2)	60 (2)	70 (3)	92	<0.001

	HF-REF					*P*-value (test for trend)	HF-PEF					*P*-value (test for trend)
Pulse pressure (mmHg)	**≤39**	**40–45**	**46–53**	**54–64**	**≥64.5**		**≤45**	**46–55**	**56–64**	**65–78**	**79–164**	
pressure (mmHg)					(11)						(14)	
LVEF %, median (IQR)	27 (20, 34)	30 (23, 37)	32 (24, 38)	33 (26, 39)	34 (27, 41)	<0.001	58 (53, 63)	58 (53, 64)	59 (54, 64)	59 (54, 66)	60 (55, 66)	<0.001
All-cause deaths, *n* (%)	1017 (27)	952 (21)	919 (23)	971 (22)	1007 (24)	0.046	128 (13)	142 (14)	153 (16)	175 (18)	220 (22)	<0.001

Distribution of pulse pressure by left ventricular ejection fraction stratum

The proportion of patients with a pulse pressure <45 mmHg differed considerably between those with HF-REF and HF-PEF (*Table 2*). Of the 22 038 patients with HF-REF, 8802 (39.9%) had a pulse pressure <45 mmHg. Of 5008 patients with HF-PEF, 1025 (20.5%) had a pulse pressure <45 mmHg. Conversely, 19.8 and 39.6% of patients with HF-REF and HF-PEF, respectively, had a pulse pressure >65 mmHg.

All-cause mortality

During 3 years follow-up, there were 4980 (23%) and 828 (17%) deaths among patients with HF-REF and HF-PEF, respectively. There was a highly significant interaction between the EF category (reduced/preserved) and the relationship between pulse pressure and mortality ($P < 0.0001$).

In patients with HF-REF, crude mortality was highest in patients in the *lowest* pulse pressure quintile although mortality differed little across the other quintiles before adjustment for other prognostic factors (*Table 2*). Mortality in Q1 (lowest) to Q5 (highest pulse pressure) was 27, 21, 23, 22 and 24%, respectively. However, after adjustment, there was a clear gradient in the risk of death according to pulse pressure quintile with the highest risk in patients with the lowest pulse pressure (*Table 3*, *Figures 1 and 2*). Compared with patients in the highest quintile, those in the lowest pulse pressure quintile had a 68% higher adjusted relative risk of death [95% confidence interval (CI) 53–84%].

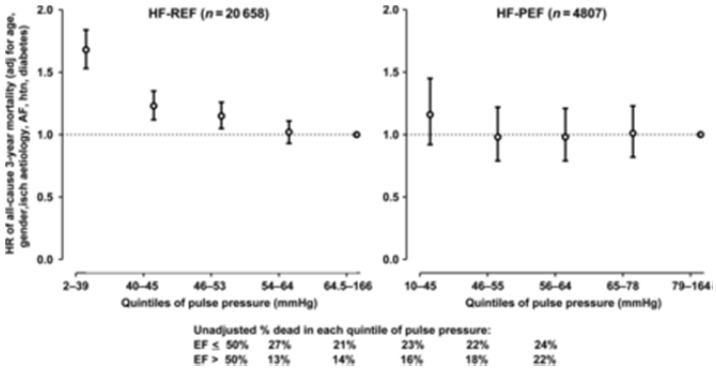
Table 3

Multivariable model by quintiles of pulse pressure in 20 658 patients with HF-REF—adjusted for the Meta-Analysis Global Group in Chronic Heart Failure variables

Variable	**HR (95% CI)**	***P*-value**
Pulse pressure (mmHg)		
≥64.5	1	
54–64	1.02 (0.93, 1.11)	0.749
46–53	1.15 (1.05, 1.26)	0.003
40–45	1.23 (1.12, 1.35)	<0.001
≤39	1.68 (1.53, 1.84)	<0.001
Age (per year increase)	1.04 (1.03, 1.04)	<0.001
Gender (male)	1.21 (1.13, 1.29)	<0.001

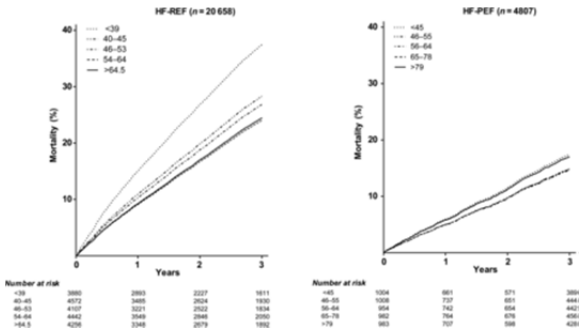
Variable	HR (95% CI)	*P*-value
Atrial fibrillation	1.21 (1.12, 1.32)	<0.001
Hypertension	0.99 (0.93, 1.05)	0.608
Ischaemic aetiology	1.12 (1.05, 1.19)	0.001
Diabetes	1.47 (1.38, 1.56)	<0.001

Figure 1.



Quintiles of pulse pressure by ejection fraction group. Adjusted for age, gender, hypertension, atrial fibrillation, ischaemic aetiology, and diabetes.

Figure 2.



Mortality curves of pulse pressure quintiles by ejection fraction group. Adjusted for age, gender, hypertension, atrial fibrillation, ischaemic aetiology, and diabetes. The curves for the pulse pressure groups of the middle three quintiles (46–55, 56–64, and 65–78 mmHg) overlap, with lower mortality compared with the highest and lowest quintiles.

Analyses that further stratified the HF-REF group into those with EF <30 and 30–49% indicated that the increase in mortality associated with low pulse pressure was particularly prominent among patients with EF <30% (see Supplementary material online, *Tables S1* and *S2*). For the patients with EF < 30%, mortality was significantly higher for patients with a pulse pressure < 54 mmHg. When analysed as continuous variables, both pulse pressure and systolic BP were independent predictors of mortality (data not shown). However, there was a significant interaction between pulse pressure and systolic BP ($P < 0.0001$), and hence the size and direction of the hazard ratio (HR) for each variable is difficult to interpret. To explore this further, a stratified analysis based on SBP <140/≥140 mmHg was conducted and this showed that patients with both a lower systolic BP (<140 mmHg) and lower pulse pressure seemed to fare particularly badly (*Table 5*).

In contrast to the patients with HF-REF, crude mortality among patients with HF-PEF was highest in those in the *highest* pulse pressure quintile and there appeared to be a gradient in crude mortality across the other quintiles before adjustment for other prognostic factors (*Table 2*). Crude mortality in Q1 (lowest) to Q5

(highest pulse pressure) was 13, 14, 16, 18 and 22%, respectively. After adjustment, however, the gradient in risk according to pulse pressure quintile in patients with HF-PEF was largely eliminated (*Table 4*, *Figures 1* and *2*). Compared with patients in the highest quintile, those in quintiles 2, 3, and 4 had an adjusted HR of ∼1.0. Those in the lowest quintile had an adjusted HR of 1.16 (95% CI 0.92, 1.45). In a similar manner to the analysis for patients with HF-REF, we explored this further with a stratified analysis based on SBP <140/≥140 mmHg, which showed that there was no significant interaction between the pulse pressure (quintiles) and the BP groups (*Table 5*).

Table 4

Multivariable model by quintiles of pulse pressure in 4807 patients with HF-PEF—adjusted for the Meta-Analysis Global Group in Chronic Heart Failure variables

Variable	**HR (95% CI)**	***P*–value**
Pulse pressure (mmHg)		
≥79	1	
65–78	1.01 (0.82, 1.23)	0.959
56–64	0.98 (0.79, 1.21)	0.836
46–55	0.98 (0.79, 1.22)	0.857
≤45	1.16 (0.92, 1.45)	0.219
Age (per year increase)	1.06 (1.05, 1.07)	<0.001
Gender (male)	1.36 (1.18, 1.57)	<0.001
Atrial fibrillation	1.15 (0.96, 1.37)	0.130
Hypertension	1.00 (0.86, 1.17)	0.977
Ischaemic aetiology	1.04 (0.90, 1.20)	0.609
Diabetes	1.61 (1.39, 1.87)	<0.001

Table 5

Analyses of quintiles of pulse pressure for HF-REF and HF-PEF, stratified by systolic blood pressure—adjusted for the Meta-Analysis Global Group in Chronic Heart Failure prognostic variables

	HF-REF				**HF-PEF**		
	Quintile of pulse pressure	**HR (95% CI)**	***P*-value**		**Quintile of pulse pressure**	**HR (95% CI)**	***P*-value**
SBP <140 mmHg (*n* = 14 039)	1	1.50 (1.20, 1.88)	<0.001	SBP <140 mmHg (*n* = 2234)	1	0.95 (0.58, 1.53)	0.823
	2	1.10 (0.88, 1.38)	0.407		2	0.73 (0.47, 1.15)	0.172
	3	1.06 (0.85, 1.33)	0.610		3	0.67 (0.43, 1.05)	0.083
	4	0.98 (0.77,	0.833		4	0.81 (0.52, 1.26)	0.347

	HF-REF				HF-PEF		
	Quintile of pulse pressure	**HR (95% CI)**	***P*-value**		**Quintile of pulse pressure**	**HR (95% CI)**	***P*-value**
		1.23)					
	5	1.0			5	1.0	
SBP ≥140 mmHg (*n* = 6619)	1	0.88 (0.39, 2.00)	0.764	SBP ≥ 140 mmHg (*n* = 2573)	1	5.66 (0.68, 47.42)	0.110
	2	1.07 (0.79, 1.44)	0.662		2	1.08 (0.50, 2.31)	0.853
	3	0.92 (0.77, 1.09)	0.322		3	1.06 (0.73, 1.55)	0.753
	4	0.89 (0.79, 1.00)	0.048		4	0.90 (0.71, 1.14)	0.373
	5	1.0			5	1.0	

Quintiles 1–5 indicate low to high pulse pressure.

When NYHA class was included in the model (see Supplementary material online, *Tables S3* and *S4*), higher NYHA class (III/IV) was associated with worse outcome [HF-REF: HR 1.87 (95% CI 1.76, 2.00); HF-PEF HR 1.99 (95% CI 1.69, 2.34)]. In patients with HF-REF, low pulse pressure remained an indepedent predictor of death even taking account of NYHA class. The relationship between pulse pressure and mortality was not altered when analyses were repeated with the addition of ACE inhibitor/angiotensin receptor antagonist, digoxin, and spironolactone treatment.

When analyses were re-run excluding patients with AF: the results for those with HF-REF were similar to the main analyses (see Supplementary material online, *Tables S5* and *S6*). The results for those with HF-PEF demonstrate that those patients with the lowest pulse pressure quintile were at increased risk (HR for lowest quintile of pulse pressure 1.33, 95% CI 1.02, 1.73).

Acute heart failure vs. chronic heart failure

The multivariable models were repeated for patients with acute HF only (see Supplementary material online, *Tables S7* and *S8*). A very similar pattern of findings was apparent although, with the reduced numbers (4746 patients compared with 25 465 for the main models) and power in this subset, mortality was significantly higher only in the lowest pulse pressure quintile in patients with HF-REF. Interestingly, in patients with acute HF-PEF, there was an increased risk with pulse pressure < 56 mmHg, although the lowest quintile group (≤45 mmHg) was of borderline significance ($P = 0.049$). The multivariable analyses were also performed for patients with chronic HF only (see Supplementary material online, *Tables S9* and *S10*). The findings were consistent with the overall model.

Discussion

This large meta-analysis is the first study to describe the range of pulse pressure and evaluate the prognostic significance of pulse pressure in patients with HF-PEF, as well as patients with HF-REF. The physiological influences on pulse pressure in HF are complex and appear to be dependent on EF, with left

ventricular function and stroke volume playing an important role in HF-REF. This is in contrast to HF-PEF where the major influence on pulse pressure is probably arterial stiffness. As has been described previously, HF-REF patients in the lowest pulse pressure quintile had the highest crude and adjusted mortality risk, compared with all other pulse pressure groups. However, the relationship among patients with HF-PEF differed: while the highest pulse pressure quintile had the highest crude mortality, this difference did not persist in the multivariable analyses.

Association between lower pulse pressure in HF-REF and increased mortality

Paradoxically, the relationship between pulse pressure and mortality appears to be reversed in HF-REF compared with that seen in patients with other cardiovascular diseases and among individuals in the general population where a high pulse pressure has consistently been linked to adverse outcomes. In populations where high pulse pressure predicts mortality risk, the cause of high pulse pressure is thought to be reduced aortic elasticity secondary to arteriosclerosis and the increased risk possibly reflects widespread arteriosclerotic disease.[11,12] However, a different pathophysiological process is evident in HF-REF where a lower pulse pressure is not an index of arterial stiffness but represents reduced cardiac function and lower stroke volume. This has recently been confirmed in an analysis from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS).[13] In a sub-study in these patients with HF-REF after myocardial infarction, pulse pressure was more dependent on left ventricular function and was not a marker of aortic stiffness, as measured by carotid-femoral pulse wave velocity. Low proportional pulse pressure (pulse pressure/systolic BP) has previously shown a correlation with a low cardiac index and stroke volume index in patients with advanced HF-REF.[14] However, the paradox in patients with HF-REF does not seem to be explained solely by measures of systolic function as studies of patients with asymptomatic left ventricular systolic dysfunction (LVSD)[15,16] have shown high pulse pressure to be predictive of mortality risk. This seems to indicate that the transition to symptomatic HF-REF in some way reverses the usual relationship between pulse pressure and outcome. Lower pulse pressure has also been associated with higher B-type natriuretic peptides (BNPs) in advanced HF-REF.[5] An additional finding in this study is that the risk associated with low pulse pressure in patients with HF-REF is especially marked in those with a lower SBP. The relationship between severity of LVSD, SBP, and outcome is complex. There is a U-shaped association between SBP and outcome in patients with less severe LVSD whereas in patients with more severe LVSD the relationship is linear, with lower SBP associated with increased mortality risk.[17] One possible (but speculative) explanation for our finding of increased mortality risk in those with low pulse pressure and lower SBP is that both of these together identify patients with a particularly low stroke volume who are at greatest mortality risk.

Pulse pressure in HF-PEF and outcome: a reverse pattern compared with HF-REF

The relationship between pulse pressure and mortality appears to be completely different among patients with HF-PEF. Analysis of crude mortality showed the reverse pattern to that observed in HF-REF, with the highest risk in those with the highest pulse pressure. At first sight this might seem to make sense as patients with HF-PEF are 'phenotypically' more similar to subjects with hypertension, or even elderly individuals in the general population, both of which have worse outcomes with higher pulse pressure. A recent analysis from the Aldosterone Receptor Blockade in Diastolic Heart Failure trial showed that higher pulse pressure was associated with higher *E*/*E*', an index of increased left ventricular filling pressure and more severe diastolic dysfunction.[18] Higher pulse pressure may be a crude surrogate of increased arterial stiffness. Increased arterial stiffness increases afterload and cardiac work and mechanistically there is a plausible link between high pulse pressure and the development of HF-PEF. However, the association between increasing pulse pressure and increasing mortality was eliminated by adjustment for other prognostic variables (whereas the association between pulse pressure and mortality was strengthened by adjustment in HF-REF). The loss of this association highlights the complexity of the condition of HF-PEF and the prognostic importance of the underlying comorbidities in the outcomes for patients with HF-PEF. The difference between crude and adjusted risk seemed to reflect the high proportion of women (61% vs. 39%) and patients with diabetes (35% vs. 19%) in the highest pulse pressure quintiles compared with the lowest

pulse pressure quintiles, two of the most powerful prognostic variables in these patients. The highest quintile also had a particularly low proportion of patients with AF and high proportion of patients with hypertension, although these were not significant predictors of mortality. Several of the prognostic variables included in the multivariable model are recognized determinants of arterial stiffness (e.g. age, sex, history of hypertension, and diabetes) and thus adjustment for these may have eliminated the significance of pulse pressure as a surrogate for arterial stiffness in HF-PEF. For patients with HF-PEF, therefore, higher pulse pressure may reflect more arterial stiffness and truly related to higher mortality. In a recent retrospective analysis of results from the Digitalis Investigator Group (DIG) trial,[19] there was a significant J-shaped relationship between pulse pressure and mortality. Interestingly in our more contemporary population of patients with HF-PEF, we found the crude mortality was highest among patients in the highest quintile (*Table 2*). However, there was no difference across the quintiles on multivariable analysis. However, in two sub-groups of patients with HF-PEF (acute HF and patients without AF), lower pulse pressure was an independent predictor of mortality. While sub-group findings must always be interpreted with caution, lower pulse pressure in these patients may also be an index of lower stroke volume. Reduced stroke volume has previously been reported in HF-PEF[20] and this may explain the J-shape relationship between pulse pressure and mortality seen in the retrospective analysis from the DIG trial.[19] These findings should be explored further in future, larger studies.

The finding of a low prevalence of AF in the highest pulse pressure quintile is curious, if not paradoxical. Higher pulse pressure is a predictor of incident AF in the general population and in patients with certain types of cardiovascular disease.[21,22] Yet we saw the opposite in relation to prevalence in patients with HF-PEF. This does not seem to be explained by difficulty in measuring pulse pressure in patients with AF as no such variation in prevalence of AF was found according to pulse pressure quintile in patients with HF-REF.

Limitations

This meta-analysis incorporated data from a large number of observational studies and randomized clinical trials, and therefore, BP measurements were not performed in a standardized fashion. Another limitation resulting from the use of a large number of observational studies and randomized clinical trials is the lack of standardization of HF diagnosis. As previously described, the variables that were incorporated into the multivariable model were selected due to their clinical relevance and because they were available in the majority of patients. Other variables, which may have prognostic significance, were not included due to the amount of missing data. Therefore, the multivariable model did not include established biomarkers, such as renal function, sodium, and haemoglobin or powerful contemporary biomarkers such as BNP. Future work should incorporate such biomarkers to evaluate the incremental prognostic value of pulse pressure. Pulse pressure may change within short time intervals and mean pulse pressure over several measurements, rather than a single measurement, may provide additional prognostic information. Central pulse pressure has been demonstrated to be a stronger prognostic marker than brachial pulse pressure in patients with hypertension[23]; however, this has never been measured in any large-scale trial in HF and was not available from any of the studies included in our analyses. A recent sub-study of EPHESUS[13] found aortic pulse wave velocity, measured by carotid-femoral pulse wave velocity, to be predictive of increased risk of cardiovascular death. The latter, a marker of increased aortic stiffness, was not available in this study but should be included in future research. Finally, the only clinical outcome available in the majority of studies was all-cause mortality and we were not able to look at non-fatal outcomes.

Conclusions

Pulse pressure is a simple, inexpensive, and readily available clinical index. This non-invasive test provides useful prognostic information for patients with HF-REF (particularly in those with an LVEF < 30%) where lower pulse pressure (especially <53 mmHg) independently predicts mortality, particularly in patients with lower systolic BP (<140 mmHg). The prognostic utility of pulse pressure among patients with HF-PEF appears more complex, with higher pulse pressure appearing to be predictive of crude but not adjusted

mortality. Future analyses evaluating the incremental prognostic value of pulse pressure, in addition to powerful contemporary biomarkers in HF, are required to determine if this simple clinical sign has a role in HF risk stratification. Such studies should include patients with HF-PEF as well as HF-REF.

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